REMARKS

I. Introduction

In response to the Office Action dated June 9, 2003, please consider the following remarks and associated exhibits. Claims 28-30 and 48-51 remain in the application. Re-examination and re-consideration of the application is requested.

II. Objections and Rejections Under 35 U.S.C. §101 and 35 U.S.C. §112, First Paragraph

On pages 2-4 of the Office Action, claims 28-30 and 48-51 were rejected under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph.

A. Claims Rejected Under 35 U.S.C. §101.

The pending claims are directed to isolated antibodies which bind to a PRO285 polypeptide, a member of the Toll protein family. Applicants' disclosure teaches that comparative homology analyses and functional data from Toll family members indicates that PRO285 polypeptide signalling activates NF-κB. Applicants' disclosure further teaches that antibodies to the PRO285 polypeptide can be used to modulate this activity. In the outstanding Office Action, the Examiner rejects the pending claims, stating that the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well established utility.

Applicants respectfully traverse this rejection.

The standard for assessing credibility of an asserted utility is articulated in the guidelines promulgated by the Patent Office for the examination of applications for compliance with the utility requirement of 35 USC 101 and 35 USC 112, first paragraph (see, e.g. 60 Fed. Reg. 36263-02). In particular, Applicants direct the Examiner's attention to the portion of section 2(a) of these guidelines which is reproduced below:

> If the applicant has asserted that the claimed invention is useful for any particular purpose (i.e. a 'specific utility') and that assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility. Credibility is to be assessed from the perspective of one of ordinary skill in the art in view of any evidence of record (e.g. data, statements, opinions, references etc.) that is relevant to the applicant's assertions.

The guidelines dictate that the appropriate standard of review involves a determination of whether the asserted utility would be considered credible by a person of ordinary skill in the art. The guidelines further state that if the assertion would be considered credible by a person of ordinary skill in the art, the Patent Office must not impose a rejection based on lack of utility. Moreover, only after the examiner has provided evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the Applicants (see, e.g. M.P.E.P. 2164.07).

In response to the Examiner's comments at page 3 of the Office Action regarding the specific function of PRO285, Applicants' direct the Examiner's attention to the portions of the specification which teach that PRO285 polypeptide signalling activates NF-κB and that antibodies to the PRO285 polypeptide can be used to modulate this activity (see, e.g. page 13, lines 13-25). This specific, substantial and credible utility is demonstrated by a number of scientific articles pertaining to the Toll polypeptide family.[1] In particular, the role that the Toll family of polypeptides play in NF-κB signalling was understood in the art, and this is shown by a review of Medzhitov et al., Nature 388, 394-397 (1997), Rock *et al.*, Proc. Natl. Acad. Sci. USA 95, 588-593 (1998) and Belvin and Anderson, Ann. Rev. Cell. Biol. 12, 393-416 (1996), all of which are cited in Applicants' specification and incorporated by reference therein. For example, Medzhitov et al.[2] teach that Drosophila and human Toll proteins contain a region of homology in their cytoplasmic domains that is associated with NF-κB signalling and that the Toll/ NF-κB host defense pathway is conserved from Drosophila to humans (see, e.g. page 396). Medzhitov et al. further teach that it is believed that the unique homology exhibited by the Toll polypeptide family results from their functional role in mediating ancient defense mechanisms that have been evolutionarily conserved in plants, insects and mammals (see, e.g. figure 1, page 394). Rock et al.[3] teach that Toll homologues are involved in innate immunity and that homology analyses of the human Toll gene family members TLR1, TLR2, TLR3, TLR4 and TLR5 and their biological association with the IL-1R-NF-κB pathway demonstrates that these Toll homologues are direct evolutionary counterparts of the

[1] It is proper to consider materials published after a critical filing date, for example when it is cited for the purpose of showing a fact under the principles of *In re Wilson*, 135 USPQ 442 (1962) (see, e.g. M.P.E.P. 2124).

[2] Medzhitov et al., is cited in Applicants specification for example at page 2, line 4.

[3] Rock et al., is cited in Applicants specification for example at page 2, line 25.

Drosophila Toll genes. Rock et al. further teach that their homology and IL-1R-NF-κB pathway association provides evidence that the biological processes associated with Toll-Dorsal/IL-1R-NF-κB pathway are shared by both Drosophila and mammals. In this context, Bevlin et al.[4] teach that "[t]hus far the only biological process common to Drosophila and mammals that uses the Toll-Dorsal/IL-1R-NF-κB pathway is innate immunity—the rapid and nonspecific response to pathogens that leads to the production of antimicrobial peptides and cytokines". Accordingly, such teachings, e.g., (1) the unique region of homology shared by Drosophila and mammalian Toll polypeptides; (2) the association between these molecules and the IL-1R-NF-κB pathway; and (3) the fact that the only biological process common to Drosophila and mammals that uses the Toll-Dorsal/IL-1R-NF-κB pathway is the innate response to microbial pathogens, supports the teaching in the present application that PRO285 polypeptide signalling activates NF-κB and that antibodies to the PRO285 polypeptide can be used to modulate this activity.

Applicants further provide a declaration under 37 CFR 1.1.32 by J. Fernando Bazan, an author of a number of articles on Toll proteins (attached herein as Exhibit A). In this declaration Dr. Bazan states that from the homology analyses of Toll proteins, including the region associated with NF-κB activity (see, e.g. Figure 7B and page 7, lines 8-23) and the functional studies with molecules having this region that demonstrate that the region is crucial for NF-κB signalling (see e.g. page 7, lines 8-23 and Example 11), one skilled in the art would reasonably understand that PRO285 can induce the activation of NF-κB and/or the expression of NF-κB-controlled genes and that antibodies to PRO285 could be made and used in accordance with routine techniques to modulate such activity.

Applicants further note that the utility of the claimed subject matter is further validated by recent reports which confirm that PRO285 (also referred to in the literature "TLR7") can induce the activation of NF-κB and/or the expression of NF-κB-controlled genes and that molecules that bind to PRO285 can be used to modulate such activity. See e.g. Jurk et al., Nature Immunology 3(6), 499 (2002) which is attached herein as Exhibit B.

For at least the reasons above, the Examiner's position that Applicants' invention lacks a specific, substantial and credible asserted utility or a well established utility is shown to be in direct

[4] Belvin et al., is cited in Applicants specification for example at page 50, line 11.

conflict with the understanding of those of skill in the art. Applicants respectfully request the withdrawal of the rejection under 35 U.S.C. §101.

B. Rejection under 35 U.S.C. §112, First Paragraph.

In rejecting the claims under 35 U.S.C. §112 at page 4 of the outstanding office action the Examiner further asserts "since the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention."

Those of skill in the art will understand from the instant application and the state of the art that Applicants' invention has a specific, substantial and credible asserted utility. Consequently, one skilled in the art clearly would in fact know how to use the claimed invention without undue experimentation. For this reason, Applicants respectfully request the withdrawal of the rejection under 35 U.S.C. §112 first paragraph.

III. Rejection under 35 U.S.C. §102(b)

On page 5 of the Office Action, claims 28 and 48 were rejected under 35 U.S.C. §102(b) as being anticipated by Ruggeri et al., WO 91/09614 (Ruggeri). The Examiner asserts that Ruggeri et al. disclose a 19 residue platelet membrane glycoprotein Ib peptide that matches SEQ ID NO: 2 at positions 704-712, a 9/15 amino acid residue match and that at page 19 and in claim 65, antibodies to such peptides are disclosed and claimed. In this context, the Examiner concludes that "antibodies of the Ruggeri disclosure would necessarily bind PRO285 due to the common 9 amino acid stretch, which is well-established in the art as being long enough to constitute an epitope". The Examiner further notes that this is anticipation via inherency and that "[I]t is not necessary that Ruggeri have any knowledge of PRO285 for anticipation to be found".

Applicants respectfully traverse this rejection. As is known in the art, polypeptides are known to fold in three dimensions and this folding ultimately defines the antigenic determinants that are recognized by antibodies. Applicants therefore traverse the outstanding rejection because the three dimensional antigenic determinant of the 19 residue platelet membrane glycoprotein Ib peptide is not necessarily present in PRO 285. In fact, textbooks on immunogenicity and antigen

structure teach that the probability that an antigenic determinant on a protein consists of only a consecutive sequence of amino acids in the primary structure is likely to be rather small.[5] Such texts further note that even if most of the determinant were a continuous sequence, other nearby residues probably play a role as well. In the instant case, a side by side comparison of nearby residues (e.g. the 6 C-terminal residues that are covalently attached to the identical 9 amino acid segments in these two polypeptides) shows the presence of two charged amino acid residues in the PRO285 protein (i.e. glutamic acid and arginine at positions 716 and 717 respectively) that are absent in the platelet membrane glycoprotein Ib peptide sequence. The significant charge differences in the C-terminal residues proximal to the shared platelet membrane glycoprotein Ib and PRO285 9 amino acid segments provides evidence that the conformations of the respective antigenic determinants in these molecules are likely to be dissimilar.

As noted above, although they share a common 9 amino acid sequence, the topography of the antigenic determinant formed by the 19 residue platelet membrane glycoprotein Ib peptide is not necessarily reproduced in the PRO285 polypeptide recited in the claims. Consequently, an antibody specific for the 19 residue platelet membrane glycoprotein Ib peptide will not necessarily bind this PRO285 polypeptide. This reference therefore fails to meet the legal requirements for a finding of anticipation via inherency. Specifically, when articulating the legal requirements for a finding of anticipation via inherency, courts state that inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." See, e.g. M.P.E.P. 2112 and *Continental Can Co. v. Monsanto Co.*, 20 USPQ 2d 1746, 1749 (Fed. Cir. 1991). Instead, to establish inherency, the extrinsic evidence "must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *Continental Can Co.*, 20 USPQ 2d 1749.

[5] See, e.g. pages 242-252 of FUNDAMENTAL IMMUNOLOGY (3rd. Ed. Raven Press) which are attached herein as Exhibit C.

As noted above, an antibody which binds a PRO285 polypeptide is not necessarily disclosed in the Ruggeri disclosure, and thus this reference fails to meet the legal requirements for anticipation via inherency. For these reasons, Applicants respectfully request the withdrawal of the rejection under 35 U.S.C. §102(b).

IV. Rejection under 35 U.S.C. §103(a)

At page 6 of the Office Action, claim 51 was rejected under 35 U.S.C. §103(a) as being unpatentable over Ruggeri in view of Coughlin, U.S. Patent No. 5,256,766 (Coughlin), and further in view of Ladner et al., U.S. Patent No. 4,946,778 (Ladner).

As the Ruggeri disclosure fails to meet the legal requirements for anticipation via inherency, this reference cannot properly be combined with U.S. Patent No. 5,256,766 and U.S. Patent No. 4,946,778 in order to suggest the subject matter recited in claim 52. For this reason, Applicants respectfully request the withdrawal of the rejection under 35 U.S.C. 103(a).

V. Conclusion

In view of the above, it is submitted that this application is now in good order for allowance and such allowance is respectfully solicited. Should the Examiner believe minor matters still remain that can be resolved in a telephone interview, the Examiner is urged to call Applicants' undersigned attorney.

Respectfully submitted,

GATES & COOPER LLP
Attorneys for Applicant(s)

Howard Hughes Center
6701 Center Drive West, Suite 1050
Los Angeles, California 90045
(310) 641-8797

By: _____
Name: William J. Wood
Reg. No.: 42,236

Date: December 9, 2003

WJW/sjm/amb